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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/849,868	05/04/2001	Wei-Qiang Gao	GENENT.035C1	1085

7590 05/15/2007

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EXAMINER	
GAMETT, DANIEL C	
ART UNIT	PAPER NUMBER
1647	
MAIL DATE	DELIVERY MODE
05/15/2007	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	09/849,868	GAO, WEI-QIANG	
	Examiner	Art Unit	
	Daniel C. Gamett, PhD	1647	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on *21 February 2007*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-12,14-17 and 19-24* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-12,14-17 and 19-24* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *02/21/2007*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 02/21/2007 has been entered.
2. Claims 1-12, 14-17, and 19-24 are under examination.
3. All prior objection/rejections not specifically maintained in this office action are hereby withdrawn.
4. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior office action.
5. Applicants' notation that proper priority for this case is not reflected in the published application, in PAIR or in the Filing Receipt is acknowledged. Steps have been taken to correct this, and Applicants should receive a corrected Filing Receipt in due course.

Claim Rejections - 35 USC § 112

6. Claims 2, 15, and 17 remain rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The rejection of record drew particular attention to the limitation "said fragments comprise amino acids numbered 226 to 266 of the corresponding heregulin sequence", now cancelled, and used the recitation of S177 of SEQ ID NO:3 as an

example of the lack of clarity that stems from inclusion of N-terminal amino acids prior to the initiator methionine in SEQ ID NO:1 and SEQ ID NO:3. The rejection also pointed out that all recitations of specific amino acid positions are unclear as they refer to SEQ ID NOS: 1 or 3. Claims 2, 15, and 17 recite specific amino acid positions in SEQ ID NO:1, which depicts the entire open reading frame of HRG-α mRNA. The initiator methionine is at position 45 in the sequence of SEQ ID NO:1. All positions less than 45 are not present in HRG-α. Therefore, the expression "HRG-α sequence of SEQ ID NO:1" is ambiguous. The HRG-α sequence of SEQ ID NO:1 consists of the sequence from positions 45 to 669. Yet claims 2, 15, and 17 recite positions 2, 3, 8, 9, 23, 24, 33, 34, 36, 37, 42, and 43. The specification does not provide clarity because these same positions are taught to be potential processing sites at [0143] and [0150].

7. Claim 9 is rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. The courts have interpreted the first paragraph of 35 U.S.C. 112 to mean that the specification must enable one skilled in the art to make and use the invention without undue experimentation. The courts have further interpreted undue experimentation as requiring "ingenuity beyond that to be expected of one of ordinary skill in the art" (Fields v. Conover, 170 USPQ 276 (CCPA 1971)) or requiring an extended period of experimentation in the absence of sufficient

direction or guidance (In re Colianni, 195 USPQ 150 (CCPA 1977)). Additionally, the courts have determined that "... where a statement is, on its face, contrary to generally accepted scientific principles", a rejection for failure to teach how to make and/or use is proper (In re Marzocchi, 169 USPQ 367 (CCPA 1971). Factors to be considered in determining whether a disclosure meets the enablement requirement of 35 U.S.C. 112, first paragraph, have been described in In re Colianni, 195 USPQ 150, 153 (CCPA 1977), have been clarified by the Board of Patent Appeals and Interferences in Ex parte Forman, 230 USPQ 546 (BPAI 1986), and are summarized in In re Wands (858 F2d 731, 737, 8 USPQ2d 1400, 1404 (Fed Cir. 1988). Among the factors are the nature of the invention, the state of the prior art, the predictability or lack thereof in the art, the amount of direction or guidance present, the presence or absence of working examples, the breadth of the claims, and the quantity of experimentation needed. The instant disclosure fails to meet the enablement requirement for the following reasons:

1) The nature of the invention: Claim 9 is drawn to a method of inducing hair cell generation or inner-ear-supporting cell growth, regeneration, and/or proliferation, comprising contacting an inner-ear-supporting cell which expresses HER2 and/or HER3 receptors with an effective amount of an isolated ligand which activates HER2 and/or HER3 receptors, wherein the isolated ligand which activates HER2 and/or HER3 receptors is a heregulin agonist antibody, wherein said heregulin agonist antibody is effective to activate a HER2 or HER3 receptor, and is an antibody raised against a heregulin polypeptide selected from the group consisting of several forms of heregulin.

Therefore, to perform the claimed method, one must first obtain an antibody that is an activating ligand for heregulin receptors by using a heregulin polypeptide as immunogen.

2) The state of the prior art and the predictability or lack thereof in the art: The art provides no basis for predicting that an antibody raised against heregulin will be a ligand (*i.e.* bind to) anything other than heregulin or other polypeptides that can be expected to share an epitope with heregulin. The art provides no evidence of sufficient amino acid sequence similarity or three-dimensional structural similarity between heregulin and HER3 (which is the ligand-binding component of HER2/3 dimers) to predict that these molecules share epitopes. Thus, a prediction that an antibody raised against heregulin will be a ligand for HER2/3 is, on its face, contrary to generally accepted scientific principles, which alone makes a rejection for failure to teach how to make and/or use the claimed invention proper (In re Marzocchi, 169 USPQ 367 (CCPA 1971). Furthermore, antibodies raised against a growth factor typically antagonize, not agonize, factor activity. For heregulin, examples of this are found in Mincione *et al.*, J. Cell. Physiol. 1998 Aug;176(2):383-391, (see Figure 6 and page 389 left column, first full paragraph) and Rosenbaum *et al.* Exp Neurol. 1997 Dec;148(2):604-615 (see Table 1 and page 610, paragraph bridging the columns).

3) The amount of direction or guidance present and the presence or absence of working examples: Enablement must be provided by the specification unless it is well known in the art. *In re Buchner* 18 USPQ 2d 1331 (Fed. Cir. 1991). The specification teaches that HER2/3 agonist antibodies may be recovered from the serum of animals immunized with HER2/HER3 or fragments thereof [0014]. This teaching is consistent with the state of the

art, as described above. The only teaching regarding the antibodies of the instant claims is a single sentence which states that such antibodies can be made: "In addition, antibodies may be selected that are capable of binding specifically to individual family members of heregulin family, e.g. HRG-.alpha., HRG-.beta.1, HRG-.beta.2, HRG-.beta.3, and which are agonists thereof" [0014].

4) The quantity of experimentation needed: It is not certain that any amount of experimentation would ever produce the antibody needed to perform the claimed method.

8. Claims 1-12, 14-17, and 19-24 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for methods comprising contacting an inner-ear-supporting cell with heregulin molecules and fragments that comprise a growth factor domain, or certain specifically defined variants thereof, does not reasonably provide enablement for all variants that have at least 80% sequence identity with the corresponding heregulin sequence or fragments comprising as little as 10 consecutive amino acid residues of the corresponding heregulin sequence. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims. Among the factors to be considered in determining whether a disclosure meets the enablement requirement of 35 U.S.C. 112, first paragraph, are the nature of the invention, the state of the prior art, the predictability or lack thereof in the art, the amount of direction or guidance present, the presence or absence of working examples, the breadth of the claims, and the quantity of

experimentation needed. The instant disclosure fails to meet the enablement requirement for the following reasons:

5) *The nature of the invention:* The claims are drawn to methods of inducing hair cell generation or inner-ear-supporting cell growth, regeneration, and/or proliferation, comprising contacting an inner-ear-supporting cell which expresses HER2 and/or HER3 receptors with an effective amount of an isolated ligand which activates HER2 and/or HER3 receptors, wherein the isolated ligand which activates HER2 and/or HER3 receptors is a a heregulin polypeptide selected from the group consisting of several forms of heregulin, variants having at least 80% sequence identity with the corresponding heregulin sequence or fragments comprising at least 10 consecutive amino acid residues of the corresponding heregulin sequence.

6) *The state of the prior art and the predictability or lack thereof in the art:* U.S. Patent 5,367,060 teaches (column 8, lines 41-50) amino acid sequence ranges that define the active growth factor domains of the various forms of heregulin. That specification gives ranges around the boundaries, but in no case is a growth factor domain taught to be less than 63 amino acids. The art recognizes that certain amino acids may be substituted in a defined way, not with any or all of the 20 natural amino acids, while heregulin activity is preserved. See, for example, US Patent 6,136,558, claim 1, which also recites "about residue 175 to about residue 230" (at least 55 amino acids) as a segment that must be conserved. Therefore, the prior art does not support the prediction that any randomly varied sequence with 80% identity to a heregulin or any fragment shorter than 55 amino acids from about residue 175 to about residue 230 will be biologically active.

7) The amount of direction or guidance present and the presence or absence of working examples: Enablement must be provided by the specification unless it is well known in the art. *In re Buchner* 18 USPQ 2d 1331 (Fed. Cir. 1991). The specification teaches [0157] several specific substitutions with the range of position 177-261. The specification implies that these same positions might be randomly substituted [0154]. The specification contemplates substitutions at sites of post-translational modification and proteolytic processing at [0139-0150]. The biological effects that form the basis for the claimed method was tested and demonstrated only with HRG-β1-177-244 (figures 9-12).

8) The breadth of the claims quantity of experimentation needed: The claims recite six different forms of heregulin, and variants of each with as little as 80% identity. It would require extensive experimentation to make and use even the embodiments of the claimed invention wherein variation at specific amino acids is suggested. Making and using the myriad polypeptides that may be 80% identical to any of the recited sequences would require undue experimentation. It is not certain that any amount of experimentation would ever enable the use of a peptide that comprises as little as 10 consecutive amino acids from the reference sequences.

9. Claims 1-12, 14-17, and 19-24 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of

the claimed invention. The fact that a patent is directed to method entailing use of a compound, rather than to the compound *per se*, does not remove patentee's obligation to provide description of the compound sufficient to distinguish infringing methods from noninfringing methods (University of Rochester v. G.D. Searle & Co., 69 USPQ2d 1886 (CAFC 2004)). To provide evidence of possession of a claimed genus, the specification must provide sufficient distinguishing identifying characteristics of the genus. The factors to be considered include disclosure of compete or partial structure, physical and/or chemical properties, functional characteristics, structure/function correlation, methods of making the claimed product, or any combination thereof. In this case, the claims are drawn to methods that require variants and fragments of heregulin molecules. With regard to "variants", claims 1-5, 7-10, 12, 14-17, and 19-22 recite a partial structural limitation in the form of 80% sequence identity. Dependent claims recite limitations to the positions that may be varied, but substitution with any amino acid is permitted, so the claims describe a very large genus of polypeptides. Claims 2, 15, and 17-21, for example, recite 126 amino acid residue positions in HRG-α that may be substituted (by any amino acid), deleted, or replaced by insertion. The substitutions alone indicate 20^{125} unique combinations in HRG-α. 20^{36} substitution variants of HRG-β are recited in claims 19-21. There are no limitations on the size, position, or number of insertions or deletions. As for 'fragments", the claims indicate that the fragments comprise a consecutive sequence of at least 10 amino acid residues of the corresponding heregulin sequence, but do not indicate what portions of the recited sequences must be preserved in any fragment. Thus, the genus of claimed heregulin polypeptides is potentially very large. The claims recite the function of activating HER2 and/or HER3

receptors, but then significant deviation from reference sequences is permitted. Accordingly, in the absence of sufficient recitation of distinguishing identifying characteristics, the specification does not provide adequate written description of the claimed genus.

10. *Vas-Cath Inc. v. Mahurkar*, 19USPQ2d 1111, clearly states that "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession *of the invention*. The invention is, for purposes of the 'written description' inquiry, *whatever is now claimed.*" (See page 1117.) The specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed." (See *Vas-Cath* at page 1116). With the exception of the specifically recited reference sequences, the skilled artisan cannot envision the detailed chemical structure of the encompassed polypeptides, and therefore conception is not achieved until reduction to practice has occurred, regardless of the complexity or simplicity of the method of isolation. Adequate written description requires more than a mere statement that it is part of the invention and reference to a potential method of isolating it. The compound itself is required. See *Fiers v. Revel*, 25 USPQ2d 1601 at 1606 (CAFC 1993) and *Amgen Inc. v. Chugai Pharmaceutical Co. Ltd.*, 18 USPQ2d 1016. One cannot describe what one has not conceived. See *Fiddes v. Baird*, 30 USPQ2d 1481 at 1483. In *Fiddes*, claims directed to mammalian FGF's were found to be unpatentable due to lack of written description for that broad class. The specification provided only the bovine sequence.

11. Applicant may look to Example 14 of the Guidelines for Written Description for guidance in drafting claims to sequence variants. Example 14 indicates that 95% identity together with a functional limitation is generally acceptable for purposes of the written description

requirement. Applicant may also note that, in the past, recitations of less than 95% identity have been allowed in claims to heregulin variants (see claim 1 of US Patent 6,136,558, for example). The allowed claims recite specific, limited substitutions that may be made at specified amino acid residues and the recited range of amino acids limits the claims to the region well known to be necessary and sufficient for receptor activation. These elements are lacking in the instant claims.

12. Therefore, only methods utilizing isolated polypeptides comprising specifically recited amino acid sequences but not the full breadth of the claim meet the written description provision of 35 U.S.C. §112, first paragraph. Applicant is reminded that *Vas-Cath* makes clear that the written description provision of 35 U.S.C. §112 is severable from its enablement provision (see page 1115).

Claim Rejections - 35 USC § 103

13. Claims 1-5, 7, 8, 10-12, 14-17, and 19-21 remain rejected under 35 U.S.C. 103(a) as being unpatentable over US Patent 6017886 (Carnahan), in view of U.S. Patent 5,367,060, issued November 22, 1994 ('060). This rejection is hereby extended to include claims 6 and 22-24. Applicant's arguments filed 02/21/2007 have been fully considered but they are not persuasive. The rejection of record holds that it would be obvious to the skilled artisan that any heregulin peptide that retains a significant portion of the EGF-like domain can stimulate utricular sensory epithelial cells. Therefore, the instant claims remain obvious insofar as they read upon in the "growth factor domain" of the various forms of heregulin described in the '060 patent. The'060 patent discloses the full amino acid sequences of Hrg-α, Hrg-β1, Hrg-

β2, Hrg-β2-like, and Hrg-β3 heregulin peptides; see Figure 15, which is identical to Figure 6 of the instant application. The '060 patent teaches the domains of each heregulin peptide that are responsible for binding to receptor at column 8, lines 42-50. As previously noted, Carnahan teaches that heregulin-β1 is one of many heregulin peptides that are effective in stimulating utricular sensory epithelial cells (see figures 3 and 5; column 9, lines 55-60). The heregulins β1, β2, β2-like, and β3 are identical through the growth factor domain. These teachings render the heregulins recited in instant claim 6 obvious. Instant claims 22-24 recite obvious embodiments of the method, as Carnahan teaches regenerating the inner ear hair cells associated with sensory epithelium and teaches *in vivo* treatment (see claim 2), which renders the cochlea is an obvious anatomical location.

14. Claims 1, 2, 10,12, 14-17 and 19-22 are rejected under 35 U.S.C. 103(a) as being unpatentable over US Patent 6017886 (Carnahan) in view of US Patent 5587458 (King) (of record). Carnahan teaches all of the target cell and intended use limitations of instant claims as noted in the rejection of claims 1, 3-8, 10, 12, 14, and 16 under 35 U.S.C. 102(e) in the office action of 07/19/2006 . The embodiments of these claims wherein the isolated ligand which activates HER2 and/or HER3 receptors is a heregulin agonist antibody directed against HER2 are obvious for the same reasons detailed in the office actions of 07/19/2006 and 12/21/2006 wherein these references were applied to reject claim 9 under 35 U.S.C. 103(a).

Conclusion

15. No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Daniel C Gamett, Ph.D., whose telephone number is 571 272 1853. The examiner can normally be reached on M-F, 8:30-5:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Brenda Brumback can be reached on 571 272 0961. The fax phone number for the organization where this application or proceeding is assigned is 571 273 8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

DCG
Art Unit 1647
11 May 2007

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